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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,954	JACOBS ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 10/23/2003. Claims 1-10 have been amended, claims 11-14 are drawn to non-elected subject matter, claims 15-20 have been added. Claims 1-20 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Foreign Priority

1. Acknowledgement of the receipt for the Finnish application 990380, filed 02/22/1999 drawn to this same subject matter has been made, in the paper received by WIPO on May 9, 2000. The filing date of the instant claims is deemed to be the filing date of the Finnish application, filed 02/22/1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-10 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the diagnosis of male infertility and for a method of screening for a genetic predisposition to male infertility characterized by detecting homozygosity for loss of the wild-type *POLG,* CAG microsatellite repeat-length allele(ie. 2

copies with the *POLG* gene mutated at the CAG microsatellite repeat with length variant other than the wild-type allele of 10 CAG repeats), **or** by detecting the heterozygote with one copy of the *POLG* gene mutated at the CAG microsatellite repeat and one copy carrying a clearly pathological mutation in the coding region of the *POLG* gene through a DNA-based molecular technique such as PCR, does not reasonably provide enablement for these methods through the detection of the presence or absence of any at least one mutation in the trinucleotide (CAG) microsatellite repeat of one allele of the *POLG* gene and the detection of the presence or absence of any at least one mutation in another allele of the POLG gene in a sample through DNA-based and immunological molecular techniques. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. Claims 1-10 and 15-20 are broadly drawn to methods of diagnosing male infertility and for a population based screening for genetic predisposition to the same by detection of the presence or absence of any at least one mutation in the trinucleotide (CAG) microsatellite repeat of one allele of the *POLG* gene and the detection of the presence or absence

of any at least one mutation in another allele of the POLG gene in a sample through DNA-based and immunological molecular techniques. The specification teaches only that those individuals found to be homozygous for loss of the wild-type *POLG* repeat-length allele(both copies mutated at the CAG repeat resulting in length variants other than the wild-type allele of 10 CAG repeats), or to be compound heterozygotes with one copy of the gene mutated at the CAG repeat allele and one copy carrying a clearly pathological mutation in the coding region of the gene, are advised that prior genetic surveys indicate that they will suffer from a fertility problem. It is only the presence of either of these above two scenarios that the method is enabled for the diagnosis of male infertility. The specification does not specify any examples of such well-established, *in–vitro* model systems or evidence for the ability of the presence or absence of any at least one mutation in the trinucleotide (CAG) microsatellite repeat of one allele of the *POLG* gene and the detection of the presence or absence of any at least one mutation in another allele of the POLG gene in a sample; wherein the presence of at least one mutation in both alleles of said POLG gene is indicative of male infertility or to a genetic predisposition to male infertility. With respect to claims 1 and 3-8 the specification teaches only that the presence of a homozygote for the microsatellite CAG repeat length mutation or the presence of a heterozygote that has one length mutation and a second mutation in the coding region of the other *POLG* allele to be diagnostic of male infertility. The specification further teaches that patients found to carry at least one wild-type copy of the gene are advised only that one common, genetic cause of male infertility has been excluded, but that this does not necessarily mean that they will be free of fertility problems, since there are other genetic and environmental causes that account for a large fraction of fertility problems. Furthermore, and with respect to claim 2, the specification teaches

only three scenarios that could prove to be predisposing to male infertility, none of these include the sole detection of any mutation or mutations, that could exist in the *POLG* gene. The specification teaches the existence of three classes of patients in Table 2, Class I(WT homozygotes), II(mutant homozygotes), and III (heterozygotes). While a result falling into Class II is an indicator of a specific type of male factor infertility(9%), a result falling into Class I does not exclude male factor infertility of other types, while a result falling into Class III is ambiguous; as it warrants further investigation to establish whether the subject represents a true heterozygote (one fully functional copy and one mutant copy of the gene) as found amongst fertile males, or whether they represent compound heterozygotes carrying one copy of the gene mutated within the *POLG* CAG repeat tract, and a second copy which has a pathological mutation in the coding region of the gene. The specification teaches that no instances of mutant homozygotes(Class II) were detected amongst fertile males, approximately 9% of infertile males, excluding cases of azoospermia and severe oligospermia, fell into Class II, and that heterozygotes (Class III) were found in all groups, but at a higher frequency in infertile than fertile males or controls. Thus, the specification only teaches that the nature of this invention relies first and foremost on the primary detection of a *POLG,* CAG microsatellite repeat-length allele that is not of the wild type length. It is necessary to also detect the other copy of the gene to determine the presence of the wild type or mutant length allele, if a homozygous mutant is detected the infertile status of the patient is known, if only one copy of the mutant, *POLG,* CAG microsatellite repeat-length allele is found though in the pair, further analysis is required on the second copy of the *POLG* allele to elucidate whether or not the second copy, although wild type for length in the CAG repeat, has a *pathological mutation in the coding region* of the gene that

could be diagnostic of male infertility. In other words, the specification only enables the detection of any pathological mutation in the coding region in *POLG,* when it is accompanied by a first detection of a mutant, *POLG,* CAG microsatellite repeat-length allele. A mutation in a *POLG* allele alone or in the coding region of the *POLG* allele alone, is not diagnostic, only if the mutation is a pathological mutation located in the coding region and is in combination with a *POLG,* CAG microsatellite repeat-length allele. With respect to claims 9 & 10 and 17 & 18, it should be noted that the specification enables only nucleotide-based detection techniques for the diagnosis of male infertility. After all, the mutation results on the nucleic acid level, and the biochemical result of any and all mutations that could be located in the *POLG* gene is highly unpredictable as each nucleic acid change could result in a multitude of conformational changes on the protein level. As a result, any attempt for the subsequent immunologic detection of a myriad assortment of mutant alleles that would result, would result in undue experimentation as it is highly unpredictable to detect any mutation or mutations in the *POLG* gene and further to detect them by immunologic methods. The nature of this invention is quite unpredictable because it requires a reliance on the prophetic testimony by applicant that the detection of the presence or absence of any mutation or multiple mutations in the *POLG* gene could be used to diagnose male infertility or as a population based screening for genetic predisposition to the same.

Scope of the invention. The scope of the invention is very broad, claiming methods for diagnosing male infertility and for a population based screening for genetic predisposition to the same by the detection of the presence or absence of any at least one mutation in the trinucleotide (CAG) microsatellite repeat of one allele of the *POLG* gene and the detection of the presence or

absence of any at least one mutation in another allele of the POLG gene in a sample through DNA-based and immunological molecular techniques. Much unpredictability exists in the broad claiming of any mutation located in a gene. The scope of the invention encompasses any and all possible mutations and any resulting conformation in the nucleic acid and later the protein imposed by these mutations being diagnostic of, or predisposing one to, male infertility. It is also important to not that "one mutation" encompasses changes in nucleic acids that do not necessarily confer a pathological phenotype. Which is to say, if one allele has the at least one mutation in the trinucleotide (CAG) microsatellite repeat of the *POLG* gene and the other allele has a mutation, but it does not confer a pathological phenotype, the method is not enabled for use a diagnostic of male infertility. The scope of the invention is even broader when considering the immunological detection of the resulting proteins whose structure is not taught in the specification and whose immunological detection would be various.

State of the art. The prior art does not disclose a method for diagnosing male infertility or for a population based screening for genetic predispostion to the same by the detection of the presence or absence of any at least one mutation in the trinucleotide (CAG) microsatellite repeat of one allele of the *POLG* gene and the detection of the presence or absence of any at least one mutation in another allele of the POLG gene in a sample through DNA-based and immunological molecular techniques, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the art for the ability of the method of detection and screening to have such far-reaching effects such as using the presence or absence of any mutation in any part of the *POLG* gene to be diagnostic of male infertility, results in the invention being unpredictable in terms of its use as presently claimed. For example, the art of Rovio et al.(EJHG 1999; 140-146)

teach that the instability of the trinucleotide repeat(CAG) in the POLG gene and teach that trinucleotides are associated with various human disorders, including Huntington's disease, myotonic dystrophy, and several forms of spinocerebellar atrophy. The reference also teaches that the disorders may be classified according to where the repeat is found in relation to the coding sequence of the gene. "Where the repeat is found in coding sequence, as here, such disorders are usually dominant, reflecting a gain of function associated with expanded repeat number. Where the repeat is found outside coding DNA, inheritance is usually recessive, reflecting loss of function and repeat expansions can be, and usually are, much larger"(141), attesting to the unpredictability then of sequences including CAG repeat tracks and the unpredictability that would ensue in claiming any mutation in any part of the *POLG* gene. The art further teaches unpredictability in the Ropp et al(Genomics1996) reference as the "presence of the trinucleotide repeat sequence in the coding region of the human DNA *POLG* gene is very puzzling considering the crucial importance of the DNA *POLG* in the biogenesis of mitochondria and especially since such trinucleotide repeat sequences, like that found in DNA *POLG* are potentially unstable, leading to expansion or contraction of the sequence(456)" Such variance in sequences with CAG repeats, known to characterize the *POLG* gene, makes the claims to any mutation in any part of the gene to be highly unpredictable as factors in addition to the sheer unpredictability of assuming all mutations are the same and result in the same phenotype exist are present making the assumption that much more tenuous.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance and working examples concerning the DNA based detection methods of examples 1-3 for positive tests resulting only with the mutant homozygote

and the composite heterozygote. Considering the unpredictability surrounding the assumption that every mutation will result in the same phenotype, as pointed out in the Nature of the invention section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention with every other mutation besides those in the CAG repeat tract of *POLG*.

Level of skill in the art. The level of skill involved in relating characteristics of such different mutations in a molecule to each other is very high if not impossible. Additionally, the functional use of such assumed similar properties from such different molecules is seen, in this instance, to be prophetic.

Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

Response to Arguments:

First, in response to applicant's assertion that "claims 7-8, 15-16 and 19-20 are consistent with this finding of enablement" the examiner finds their scope to still be broader than that which is enabled as can be seen above in the revised enablement rejection made in response to applicants' amendments to the claims. In response to applicant's second point concerning the enablement of claims 9 and 10 drawn to methods of detection involving protein based techniques, although the examiner acknowledges that a person well skilled in the art would be able to detect known mutations through these asserted protein-based biochemical techniques, it remains highly unpredictable in this case, as each nucleic acid change could result in a multitude of

conformational changes on the protein level. As a result, any attempt for the subsequent immunologic detection of a myriad assortment of resulting mutant alleles, would result in undue experimentation as it is highly unpredictable to detect any mutation or mutations in the *POLG* gene and further to detect them by immunologic methods.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (571)272-0748. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in

charge of the prosecution of this case, Carla Myers, can be reached at (571)272-0747. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782. The official fax number is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (571)272-0518.

01/21/2004

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER